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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/924,841	08/08/2001	David R. Dilley	MSU 4.1-560	2882

21036 7590 12/16/2004

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EXAMINER	
PAK, YONG D	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 12/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/924,841	DILLEY ET AL.	
	Examiner	Art Unit	
	Yong D Pak	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *4-6,13-15 and 19-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,7-12 and 16-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/8/2001*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-50 are pending. Claims 4-6, 13-15 and 19-50 are withdrawn. Claims 1-3, 7-12 and 16-18, drawn to an IPNS of SEQ ID NO:1, are under consideration

Election/Restrictions

Applicant's election without traverse of Group I and a further election of an IPNS of SEQ ID NO:1 in the reply filed on September 27, 2004 is acknowledged.

Claims 4-6, 13-15 and 19-50 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on September 27, 2004.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on August 8, 2001 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Drawings

Drawings submitted in this application are accepted by the Examiner for examination purposes only.

Claim Objections

Claims 3 and 12 are objected for being drawn to non-elected products, SEQ ID NOs: 2-10.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2 and claims 3 and 7-9 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-2 recite the term "genes". The metes and bounds of the phrase in the context of the above claim is not clear to the Examiner. A gene comprises of a coding sequence and introns, exons and regulatory sequences. A perusal of the specification did not provide the Examiner with a specific definition for the above phrase. Therefore, it is not clear whether the above term in said claims encompass the intronic and regulatory sequences or is limited to a cDNA. Examiner suggests replacing the above term with "polynucleotides".

Claim 1 and claims 2-3 and 7-9 depending therefrom and claim 10 and claims 11-12 and 16-18 depending therefrom are rejected under 35 U.S.C. 112, second

paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1 and 10, the phrase "amino acid residue two amino acid residues upstream of a histidines residue which is an iron ligand of the enzyme" is unclear because some IPNS have two histidines residues which is an iron ligand of the enzyme. Therefore, it is not clear whether the claims are drawn to a mutant IPNS having two mutations or only one mutation.

Also, without providing the specific amino acid residue number of the enzyme, it would not be possible for one of ordinary skill in the art to determine as to which specific histidines is involved in iron binding and that it would also be impossible for the Examiner to do a meaningful search.

Claim 2 and claims 3 and 7-9 depending therefrom and claim 11 and claims 12 and 16-18 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 2 and 3, the phrase "encoding an isopenicillin N synthetase (IPNS) activity" is not clear. A polynucleotide encodes a protein, not a protein "activity".

Claims 3 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 3 and 12, the phrase "IPNS activity comprises the amino acid sequence selected from .." is unclear. An amino acid sequence of a protein is not an "activity" of that protein, but is a description of the protein's structure.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 7-11 and 16-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1 and 7-9 are drawn to a modified organism comprising a polynucleotide encoding a non-heme (II) dependent family of oxygenases and oxidases wherein the protein has a mutation at an amino acid residue two residues upstream of a histidine residue which is an iron ligand of the protein. Claims 10 and 14 are drawn to a polynucleotide encoding a non-heme (II) dependent family of oxygenases and oxidases wherein the protein has a mutation at an amino acid residue two residues upstream of a histidine residue which is an iron ligand of the protein. Claims 2 and 11 limit the non-heme (II) dependent family of oxygenases and oxidases to an isopenicillin N synthetase (IPNS). These claims encompass recombinant organisms comprising variants and

mutants of any non-heme (II) dependent family of oxygenases and oxidases and IPNS . Therefore, the claim is drawn to modified organisms comprising a genus of polynucleotides encoding polypeptides having any structure. Although the specification describes non-heme (II) dependent family of oxygenases and oxidases comprising the recited mutation (SEQ ID NO:1 wherein Glu212Arg), the specification is limited to a IPNS and DAOCS. The description of just these two species is not enough to describe the whole genus of a non-heme (II) dependent family of oxygenases and oxidases and there is no evidence on the record of the relationship between the structure of IPNS and DAOCS and the structure of any recombinants, variants and mutants of non-heme (II) dependent family of oxygenases and oxidases or any recombinants, variants and mutants IPNS. The specification also does not describe which residues of a non-heme (II) dependent family of oxygenases and oxidases or IPNS are needed to impart a variant or mutant with non-heme (II) dependent family of oxygenases and oxidases or IPNS activity. Therefore, the specification fails to describe a representative species of the genus comprising variants and mutants of any non-heme (II) dependent family of oxygenases and oxidases or IPNS.

Given this lack of description of the representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the inventions of claims 1-2, 7-11 and 16-18.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1-2, 7-11 and 16-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant microorganism transformed with a polynucleotide encoding a mutant of IPNS of SEQ ID NO:2, wherein residue at position 212 of SEQ ID NO:2 is substituted with an arginine residue, does not reasonably provide enablement for transforming any "organism" with a polynucleotide encoding any mutants and variants of non-heme (II) dependent family of oxygenases and oxidases or IPNS comprising a mutation at a residue two residues upstream from a histidines residue binding to an iron. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1, 7-10 and 16-18 are drawn to "organisms" comprising any polynucleotide encoding a non-heme (II) dependent family of oxygenases and oxidases wherein the protein has a mutation at an amino acid residue two residues upstream of a histidine residue which is an iron ligand of the protein. Claims 2 and 11 limit the non-heme (II) dependent family of oxygenases and oxidases to a isopenicillin N synthetase (IPNS). Therefore, the claims encompass polynucleotides encoding recombinants, variants and mutants of any non-heme (II) dependent family of oxygenases and oxidases or IPNS, wherein the residue which is two residues upstream from a histidines residue binding to an iron, is modified. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotides encoding variants and mutants of any non-heme (II) dependent family of oxygenases and oxidases to a isopenicillin N synthetase (IPNS), broadly encompassed by the claims. Since applicants have only shown the transformation of a fungal host cell and since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to transformation of any "organisms" and with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to a modified fungal cells comprising a mutant of an IPNS of SEQ ID NOs: 1, wherein residue at position 212 has been

substituted with an arginine residue. It would require undue experimentation of the skilled artisan to make and use the claimed modified organisms comprising the variants and mutants of any non-heme (II) dependent family of oxygenases and oxidases to a isopenicillin N synthetase (IPNS). In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure, the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While enzyme isolation techniques, recombinant (i.e. transformation and transfection) and mutagenesis techniques are known, and it is routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. Similarly, transformation of any or all organisms with a polynucleotide is limited and unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompasses modifying any or all organisms with mutants and variants of any non-heme (II) dependent family of oxygenases and oxidases to a isopenicillin N synthetase

(IPNS), because the specification does not establish: (A) a universal single method for modifying any or all "organism" for producing an antibiotic; (B) regions of the protein structure which may be modified without affecting non-heme (II) dependent family of oxygenases and oxidases or IPNS activity or render the mutant enzyme with dependency on bicarbonate as an activator to produce an antibiotic; (C) the general tolerance of non-heme (II) dependent family of oxygenases and oxidases or IPNS to modification and extent of such tolerance; (D) a rational and predictable scheme for modifying any amino acid residue with an expectation of obtaining the desired biological function; and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including polynucleotides encoding variants and mutants of any non-heme (II) dependent family of oxygenases and oxidases or IPNS. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of mutants and variants of any non-heme (II) dependent family of oxygenases and oxidases or IPNS having the desired biological characteristics recited in the claim is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 9 and 18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that the microorganisms (Streptomyces sp. 0A-6129 and Streptomyces sp. KC-6643) is/are required to practice the claimed invention. As a required element it/they must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it/they is/are not so obtainable or available, the enablement requirements of 35 U.S.C. § 112, first paragraph, may be satisfied by a deposit of the microorganism(s). See 37 C.F.R. § 1.802.

The specification does not provide a repeatable process for obtaining the microorganism(s) and it is not apparent if the microorganism(s) is/are readily available to the public. The specification must contain the date that the microorganism(s) was/were deposited, the name of the microorganism(s) and the address of where the microorganism(s) was/were deposited.

If the deposit(s) has/have been made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his/her signature, and registration number, stating that the specific strain(s) has/have been deposited under the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably

removed upon the granting of a patent, would satisfy the deposit requirements. See 37 C.F.R. § 1.808.

If the deposit(s) has/have not been made under the Budapest Treaty, then in order to certify that the deposit(s) meets the criteria set forth in 37 C.F.R. § 1.801-1.809, Applicant(s) may provide assurance of compliance by an affidavit or declaration, or by a statement by an Attorney of record over his/her signature and registration number, showing that:(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;(c) the deposit(s) will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer;(d) a viability statement in accordance with the provisions of 37 C.F.R. § 1.807; and (e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition, the identifying information set forth in 37 C.F.R. § 1.809 (d) should be added to the specification. See 37 C.F.R. § 1.803-1.809 for additional explanation of these requirements.

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935.

The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Yong D. Pak
Patent Examiner 1652

Rao Manjunath
Primary Examiner 1652